REMARKS

A. Regarding the Amendments

Claims 1-6, 8 and 16 have been amended merely to claim the invention with greater precision and particularity. Claims 7, 9, and 11-15 have been canceled without prejudice. For the purposes of rejoinder under M.P.E.P. 821.04 which the Applicant had previously requested and which request is now repeated, the withdrawn claim 10 has been also amended.

No new matter has been introduced by the claims amendments or by the specification amendments. In particular, claim 1, as amended, now recites "a vaccine preparation," which was recited by the canceled claim 7. Claim 1, as amended, also recites "an adjuvant" which was recited previously by claim 1 and "an antigen" which was recited by the canceled claim 9 and amended claim 16. These limitation are disclosed in the originally filed application (see, page 10, lines 7-12; page 14, lines 15-24; page 11, lines 4-20; and working Examples 3-5 and 7-17 on pages 19-30). Claim 16 has been amended to limit the pathogenic organisms to those which were found enabled (page 2 of the Office Action, item 3, first three lines).

B. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 9 and 16 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled (item 3, pages 2-7 of the Office Action). The rejection is respectfully traversed.

More particularly, the Examiner has repeated the previous assertion that the specification does not enable vaccine preparations for *Helicobacter pylori*, enterohaemorrhagic *Escherichia coli* (EHEC), *Chlamydia*, *Mycoplasma*, *Plasmodium*, coccidium, and schistosome. The Examiner has also commented that in order to rely on the "treatment" meaning of the term "vaccine," the language of claim 9 has to reflect such a meaning (page 6, lines 6-13 of the Office Action).

The Applicants have canceled claim 9 without prejudice.

With respect to claim 16, the Examiner conceded that claim 16 is enabled with respect to each of influenza virus, rotavirus, measles virus, rubella virus, mumps virus, *Bordetella pertussis*, and diphtheria bacillus (page 2 of the Office Action, item 3, first three lines). The Examiner has also conceded that claims are enabled with respect to hepatitis B virus (page 5, lines 8-9 of the Office Action). The Applicant has amended claim 16 to limit the pathogenic organisms only to those with respect to which claim 16 was found enabled, as conceded by the Examiner. Accordingly it is submitted that the subject matter claimed in claim 16 is completely enabled, with respect to the traditional (i.e., "prevention") meaning of the term "vaccine." Therefore, it is not necessary to further define "vaccine" in claim 16 as in claim 9.

Accordingly, it is submitted that the rejection under 35 U.S.C. § 112, first paragraph does not apply to claims 9 and 16. Withdrawal of the rejection and reconsideration are respectfully requested.

C. Rejection Under 35 U.S.C. § 102 (b)

Claims 1-6 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Sakuma et al. (Chem. Pharm. Bull., 1981, 30(3):810-821) ("Sakuma II"), (item 5, pages 7-8 of the Office Action). This rejection is respectfully traversed.

The applicant has amended claims 1-6 to recite "a vaccine preparation" corresponding to the identical subject matter of the now canceled claim 7. "An adjuvant" and "an antigen" as are further recited by claims 1-6.

It is submitted that Sakuma II fails, explicitly or inherently, to describe the vaccine preparation which comprises one or more antigens as a vaccine, and one or more onjisaponins of the present invention, as recited by claim 1. Sakuma II describes just a method of chemical determination of the structure of various onjisaponins. Sakuma II is silent with respect as to how or which onjisaponins can be used, or what else (besides onjisaponins E, F, and G) may be contained in such vaccine preparation.

In view of the foregoing, claim 1 is patentably distinguishable over Sakuma II. Each of claims 2-6 depends on claim 1 and is considered patentable at least for the same reasons. Withdrawal of the rejection and reconsideration are respectfully requested.

D. Rejection Under 35 U.S.C. § 103 (a)

Claims 7-9 and 16 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Sakuma II in view of Kensil (Critical Reviews in Therapeutic Drug Carrier Systems, 1996, 13(1/2):1-55 (item 7 on pages 8-10 of the Office Action). This rejection is respectfully traversed.

Claims 7 and 9 have now been canceled. Claims 2-6, 8 and 16 have been amended and now depend from claim 1. Accordingly, the rejection has now been directed to the subject matter claimed in the amended claims 1-6, 8, and 16.

As pointed out in the previous response, to establish a *prima facie* case of obviousness over a combination of references, the combination of references must teach or suggest all of the claim limitations. The Applicants respectfully reiterate that the combination of references neither teaches nor suggests every limitation of claim 1. Accordingly, the above requirement for establishing a *prima facie* case of obviousness has not been satisfied.

As discussed above, Sakuma II fails to disclose a vaccine preparation comprising one or more onjisaponins as recited in claim 1. Kensil fails to cure this deficiency. Indeed, the Kensil reference neither discloses nor suggests saponin compounds having a presenegenin skeleton and use of the compounds as a vaccine of the present invention. More specifically, Kensil teaches using different kind of saponins (QS-7, QS-17, QS-18 and QS-21) isolated from the partial Quil A preparations for an adjuvant activity, as discussed in the previous response. Nor is there any suggestion in Kensil to replace any of saponins QS-7, QS-17, QS-18 and QS-21 with any of onjisaponins E, F, and G as described in Sakuma II, because Kensil does not provide any motivation to make such replacement.

Indeed, saponins in Kensil all have the aldehyde at position 4 of the quillalic acid, and Kensil teaches that the presence of the aldehyde group is "critical" for the saponin to be adjuvant-active (see, page 42, lines 10). The importance of the presence of the aldehyde group was especially stressed by Kensil since his experiments have shown that the adjuvant activity was lost when the aldehyde group was blocked. As previously discussed none of the onjisaponins recited in the claims of this application has the presenegenin skeleton that includes the aldehyde group at position 23 (corresponding to position 4 of the representative structure in Figure 6 of Kensil reference).

It is axiomatic that the physical, chemical and other properties of a compound directly depend on the compound's chemical structure (i.e., on the presence or absence of particular functional groups in the compound's molecule). Thus, there is a reasonable expectation that due to the presence of the aldehyde group, saponins QS-7, QS-17, QS-18 and QS-21 would evince a kind of behavior that is different from that exhibited by onjisaponins (e.g., onjisaponins E, F, and G), which do not have the aldehyde group, but have a carboxyl group instead.

Clearly, the substitution of saponins taught by Kensil (having aldehyde groups) with onjisaponins, as in claim 1 (no aldehyde groups) is highly non-obvious since Kensil not only shows saponins with aldehyde groups but goes even further by emphasizing that to have aldehyde groups is "critical." Accordingly, one skilled in the art trying to prepare saponin-based adjuvant composition will be motivated to have a saponin with the aldehyde group, and dissuaded from using a saponin without aldehyde groups.

Therefore, Kensil reference neither discloses nor suggests saponin compounds having a presenegenin skeleton and use of the compounds as a vaccine as provided in claim 1. The specification states (page 8, lines 19-28):

> *"It is impossible to predict that saponins having the above-mentioned structure exhibit the strong adjuvant activity even based on descriptions in previous reports. For example, a study on the correlation between structure*

and activity for QS-21 has shown that the 23-aldehyde on the quillaic acid skeleton plays an important role in the onset of the activity (S. Soltysik, J.-Y. Wu, J. Recchia, D.A. Wheeler, M.J. Newman, R.T. Coughlin and C.R. Kensil, Vaccine, 13, 1403-1410, 1995). However, despite the fact that the saponins of the present invention have no aldehyde group but a carboxyl group at position 23, they have high adjuvant activities. This novel finding was eventually revealed based on the results of studies for long years by the present inventors."

Accordingly, the Applicant have clearly reversed the conclusion by Kensil et al. that an aldehyde group at position 23 (corresponding to position 4 of the representative structure in Figure 6 of the Kensil reference) plays an important role for adjuvant activity. Indeed, the compounds of the present invention exhibit unexpectedly superior properties compared to what should be expected based on the teachings of Kensil.

As described in the present application (page 3, lines 20-24), saponins generally exhibit strong hemolytic activity. The hemolysis causes side effects including anemia, organ malfunctions, malnutrition, thrombosis, and others. Therefore, particularly when administrated by injection, saponin can cause the problems.

As described in Example 6 (page 23, line 19 to page 24, line 5) of the present application, the Applicants have performed the hemolytic test of the onjisaponins E, F and G relating to the present invention, according to the often used protocol using sheep erythrocytes (SRBC: sheep red blood cell). Surprisingly, as shown in Figure 6 in the present application, no hemolytic activity was found for all the onjisaponins E, F and G at the concentration of 100 μg/ml. Furthermore, even at higher dose of 200 μg/ml, the onjisaponins E, F and G showed no or little hemolytic activity.

On the other hand, as demonstrated in Pillion et al (J. Pharm. Sci., Vol.85, No.5, 1996, page 518-524), a copy of which is submitted herewith, *Quillaja* saponins such as QS21 and QS18 as described in Kensil reference have very strong hemolytic activity. The authors

conducted the hemolytic test according to substantially identical protocol using SRBC (page 520, left column, lines 25-39) and the data obtained has been shown in Figure 5B (page 522). QS-21 and QS-18 showed almost 100% maximum hemolysis at the concentrations of 20μM and 30μM, respectively, which correspond to 40μg/ml and 64μg/ml, respectively since molecular weights of the QS-21 and QS-18 are 1989 and 2151, respectively (page 519, Figure 1 of Pillion et al.).

Accordingly, whereas the *Quillaja* saponins such as QS21 and QS18 as described in Kensil reference bring about a very strong adverse effect, the onjisaponin compounds which compose a vaccine preparation as an adjuvant provide much safety for clinical application.

Accordingly, even if Sakuma II and and Kensil references are combined, the combination fails to disclose every limitation of claim 1, thus making claim 1 non-obvious over the combination of the two references. Each of claims 2-6, 8 and 16 depends on claim 1 and is considered patentable at least for the same reasons. Withdrawal of the rejection and reconsideration are respectfully requested.

E. Request for Rejoinder.

Claims 1-6, 8 and 16 are directed to a composition of matter, and claim 10 is directed to method of using this composition. The Applicants respectfully renew their request for rejoinder of the withdrawn claim 10, as discussed in the previous response, as per MPEP 821.04.

As discussed above, claims 1-6, 8 and 16 are allowable, and claim 10 includes all the limitations of the patentable product claimed in claims 1-6, 8 and 16. Accordingly, the Applicants respectfully request that claim 10 be rejoined at this time.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Check No. 579170 in the amount of $180.00 is enclosed for the submission of the Information Disclosure Statement. However, if any fee is due, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,

Date: September 14, 2005

Lisa A. Haile, J.D., Ph.D.
Registration No.: 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER No. 28213